General

Guideline Title

Recommendations for drug therapies for relapsing-remitting multiple sclerosis.

Bibliographic Source(s)

Canadian Agency for Drugs and Technologies in Health (CADTH). Recommendations for drug therapies for relapsing-remitting multiple sclerosis. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health (CADTH); 2013 Oct. 19 p. [44 references]

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Recommendation 1: The Canadian Drug Expert Committee (CDEC) recommends glatiramer acetate or interferon beta-1b as the initial pharmacotherapies of choice for patients with relapsing-remitting multiple sclerosis (RRMS).

Of Note

1. The cost-effectiveness results are unfavourable for all available pharmacotherapies included in the pharmacoeconomic model except interferon beta-1b and glatiramer acetate.
2. Subcutaneous interferon beta-1b is available as more than one brand name product. CDEC noted that the choice of interferon beta-1b product funded by drug plans should be based on price.
3. Compared with placebo, subcutaneous interferons beta-1a 44 mcg and beta-1b 250 mcg produced similar reductions in the annualized relapse rate, based on both direct and indirect evidence; however, interferon beta-1a 44 mcg was more costly.
4. Intramuscular interferon beta-1a 30 mcg was considered to be less efficacious, as assessed by the annualized relapse rate, compared with subcutaneous interferons beta-1b 250 mcg and beta-1a 44 mcg, based on both direct and indirect evidence. The cost of interferon beta-1a 30 mcg is more than interferon beta-1b 250 mcg, but less than the cost of interferon beta-1a 44 mcg.
5. At the manufacturer-provided price for the Therapeutic Review, dimethyl fumarate is not a cost-effective option for initial treatment of RRMS.

Reasons for Recommendation 1

- The clinical evidence suggests that glatiramer acetate and interferon beta-1b have statistically significant and clinically meaningful effects on the annualized relapse rate relative to placebo (relative rates of 0.67), and are the most cost-effective initial pharmacotherapies for treatment

of RRMS.
- Results of the probabilistic sensitivity analysis indicate that there is considerable uncertainty regarding whether glatiramer acetate is the most cost-effective treatment; interferon beta-1b may also be the most cost-effective treatment.

Recommendation 2: CDEC recommends that patients with RRMS who have failed to respond to, or have contraindications to, glatiramer acetate as the initial treatment be treated with interferon beta-1b. Similarly, CDEC recommends that patients with RRMS who have failed to respond to, or have contraindications to, interferon-beta-1b as the initial treatment be treated with glatiramer acetate.

Recommendation 3: CDEC recommends that subsequent pharmacotherapies for patients with RRMS who have failed to respond to, or have contraindications to, glatiramer acetate and interferon beta-1b be selected from dimethyl fumarate, fingolimod, and natalizumab. The selection should be based on cost and individual safety concerns.

Of Note

1. Most of the included trials did not distinguish between initial therapy and subsequent therapy and enrolled both treatment-experienced and treatment-naïve patients. Therefore, these recommendations are premised on the assumption that the relative efficacy will not change by the sequence in therapy.
2. With regard to the aforementioned recommendations, patients with RRMS previously or currently treated with interferon beta-1a who fail to respond do not require a trial of interferon beta-1b to be eligible for treatment with one of dimethyl fumarate, fingolimod, or natalizumab.
3. Evolving safety considerations may influence the choice of subsequent pharmacotherapies in patients with RRMS who have failed to respond to, or have contraindications to, both glatiramer acetate and interferon beta-1b.
4. CDEC considered the importance of having a wide selection of effective treatments available to patients and practitioners. The recommendations strike a balance between providing choice of both initial and subsequent treatments, while considering the relative cost-effectiveness of treatments.

Reason for Recommendation 2

Interferon beta-1b and glatiramer acetate had similar efficacy, as assessed by the annualized relapse rate, based on both direct and indirect evidence, but belong to different therapeutic classes.

Reason for Recommendation 3

Dimethyl fumarate, fingolimod, and natalizumab were not cost-effective as initial treatment, and there were insufficient data to determine their relative efficacy and cost-effectiveness as sequential treatments.

Recommendation 4: CDEC recommends that combination therapy for treatment of RRMS not be used.

Of Note

While combination therapies resulted in some radiological improvements, the clinical significance of these improvements is uncertain.

Reason for Recommendation 4

The systematic review demonstrated no clinical advantage of combination therapy over monotherapy for RRMS.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Relapsing-remitting multiple sclerosis (RRMS)

Guideline Category

Assessment of Therapeutic Effectiveness

Management

Treatment

Clinical Specialty

Family Practice

Internal Medicine

Neurology

Pharmacology

Intended Users

Advanced Practice Nurses

Health Care Providers

Health Plans

Hospitals

Managed Care Organizations

Nurses

Pharmacists

Physician Assistants

Physicians

Public Health Departments

Utilization Management

Guideline Objective(s)

To provide recommendations regarding the use of pharmacological treatment strategies, both alone and in combination, for relapsing-remitting multiple sclerosis (RRMS)

Target Population

Patients diagnosed with relapsing-remitting multiple sclerosis (RRMS)

Interventions and Practices Considered

1. Glatiramer acetate
2. Interferon beta-1b
3. Interferon beta-1a
4. Dimethyl fumarate
5. Fingolimod
6. Natalizumab

7. Combination therapy (not recommended)

Major Outcomes Considered

- Clinical efficacy of treatments
- Relapse
- Disability
- Magnetic resonance imaging (MRI) changes (e.g., lesions)
- Quality of life
- Mortality
- Safety events (e.g., death, serious adverse events, total adverse events, and discontinuation due to adverse events)
- Cost-effectiveness/clinical utility of treatments

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Searches of Unpublished Data

Description of Methods Used to Collect/Select the Evidence

The evidence for developing the recommendations was derived from the Canadian Agency for Drugs and Technologies in Health (CADTH) therapeutic review report titled *Comparative clinical and cost-effectiveness of drug therapies for relapsing-remitting multiple sclerosis* (see the "Availability of Companion Documents" field) and from patient group input to CADTH submitted by the Multiple Sclerosis Society of Canada.

Research Questions

1. What is the comparative efficacy and safety between individual disease-modifying agents in relapsing-remitting multiple sclerosis (RRMS)?
2. What is the comparative cost-effectiveness between individual disease-modifying agents in RRMS?
3. What is the comparative efficacy and safety of combination therapy (two or more disease-modifying agents compared with individual agents or other combinations) in RRMS?
4. What is the comparative cost-effectiveness of combination therapy (two or more disease-modifying agents compared with individual agents or other combinations) in RRMS?

Literature Search Strategy

The literature search was performed by an information specialist using a peer-reviewed search strategy (Appendix 3 of the clinical and economic report [see the "Availability of Companion Documents" field]).

Published literature was identified by searching the following bibliographic databases: MEDLINE with In-Process records and daily updates via Ovid; EMBASE via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were relapsing-remitting multiple sclerosis and interferon beta-1a/1b, natalizumab, glatiramer acetate, fingolimod, teriflunomide, dimethyl fumarate, and alemtuzumab.

Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials (RCTs), and safety studies. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year but was limited to English language results. Conference abstracts were excluded from the search results.

The initial search was completed on November 9th, 2012. Regular alerts were established to update the search until October 2013. Regular

search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant sections of the Grey Matters checklist (http://www.cadth.ca/resources/grey-matters), which includes the websites of regulatory agencies, health technology assessment agencies, clinical trial registries, and professional associations. Google and other Internet search engines were used to search for additional web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts.

Selection Criteria and Methods

Trials were included in the systematic review based on the pre-specified selection criteria (see Table 2 of the clinical and economic report [see the "Availability of Companion Documents" field]). Active and placebo-controlled trials were selected for inclusion if they were published in English, involved patients with RRMS, had treatment arms consisting of currently available or emerging disease-modifying agents, and reported any of the specified outcomes related to clinical efficacy and safety. Trials that included mixed populations of MS were also included if the proportion of RRMS patients was more than 50% of the total population. For interventions currently approved by Health Canada for the treatment of RRMS, only approved formulations and doses were included in the systematic review. Interventions not yet approved by Health Canada for the treatment of RRMS, but expected to enter the Canadian market shortly, were not restricted to specific doses or formulations. Studies were excluded if they were published in languages other than English; were non-randomized, follow-up or extension studies; or reported preliminary results in abstract form.

Two reviewers independently screened titles and abstracts relevant to the clinical research questions regarding available and emerging agents for the treatment of patients with RRMS. Full texts of potentially relevant articles were retrieved and independently assessed for possible inclusion based on the pre-determined selection criteria. The two reviewers then compared their chosen included and excluded studies; disagreements were discussed until consensus was reached. The study selection process was presented in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart (see Appendix 6 in the clinical and economic report [see the "Availability of Companion Documents" field]).

Number of Source Documents

The original literature search identified 1,471 citations. Upon screening the titles and abstracts, 126 potentially relevant publications were retrieved for further scrutiny, as well as 45 additional references identified through other sources. Of the 171 potentially relevant reports, a total of 68 reports describing 30 unique studies were selected for inclusion. There were 27 studies that provided comparisons of monotherapies, and four that provided comparisons between combination therapy and monotherapy.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Meta-Analysis of Randomized Controlled Trials

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

The evidence for developing the recommendations was derived from the Canadian Agency for Drugs and Technologies in Health (CADTH) therapeutic review report titled *Comparative clinical and cost-effectiveness of drug therapies for relapsing-remitting multiple sclerosis* (see

the "Availability of Companion Documents" field) and from patient group input to CADTH submitted by the Multiple Sclerosis Society of Canada.

Data Extraction Strategy and Critical Appraisal of Included Studies

One reviewer performed data extraction for each article, using a pre-drafted data extraction form covering the following items:

- Baseline characteristics of trial participants
- Interventions evaluated, including dose, duration, and mode of administration
- Efficacy and safety results for specified outcomes
- Type of analysis (intention to treat [ITT] or per-protocol)

All extracted data were checked for accuracy by a second reviewer. Any disagreements were resolved through discussion until consensus was reached. A quality assessment of randomized controlled trials (RCTs) was performed independently by two reviewers using a standardized table based on major items from the Scottish Intercollegiate Guidelines Network (SIGN-50) instrument for internal validity. Additional critical appraisal was performed based on input from clinical experts.

Clinical outcomes included relapse (annualized relapse rate [ARR] and proportion of patients remaining relapse-free) and disability (proportion of patients with sustained disability progression, mean change of Expanded Disability Status Scale [EDSS], and mean change of Multiple Sclerosis Functional Composite [MSFC]). Disability is measured by EDSS change. The definitions of relapse and sustained disability progression from individual studies are presented in Appendix 9 in the clinical and economic report (see the "Availability of Companion Documents" field). MSFC comprises the average of the scores on the timed 25-foot walk, the nine-hole peg test, and the paced auditory serial-addition test with a three-second interstimulus interval, with higher scores (Z-score) representing improvement.

Magnetic resonance imaging (MRI) outcomes included a proportion of patients with gadolinium-enhancing (GdE) lesions, mean number of GdE lesions, proportion of patients with new or enlarging T2-hyperintense lesions, and mean number of new or enlarging T2-hyperintense lesions.

Safety outcomes included serious adverse events, discontinuation of treatment because of serious adverse events, total withdrawal, and common adverse events.

Data Analysis Methods

Direct pairwise meta-analyses were performed for all outcomes to assess consistency with network meta-analysis (NMA) results when NMA was undertaken, and to obtain summary estimates for outcomes that were not analyzed by NMA.

Review Manager 4.2 was used for all statistical analyses of direct comparisons of dichotomous and continuous outcomes in the clinical review. Where the quantitative pooling of results was appropriate, the random-effects model was used to compute treatment efficacy between interventions across studies, based on the assumption that treatment effects follow a distribution across studies.

Dichotomous data were summarized using relative risk (or risk ratio), which compares the proportion of patients having the event between two treatment groups. In this study, the dichotomous outcomes that were measured included:

- Proportion of patients who were relapse-free
- Proportion of patients with sustained disability progression
- Proportion of patients with GdE lesions
- Proportion of patients with new or enlarging T2-hyperintense lesions

Continuous data with means and standard deviations were summarized using mean differences. Where standard deviations were not reported, they were obtained from standard errors, confidence intervals, t values, or *P* values. Where no variance was reported, a value of standard deviation was imputed using the coefficient of variation, which was calculated based on studies with similar population, study design, and intervention. The continuous outcomes that were measured in this study included:

- Mean change in EDSS from baseline
- Mean change in MSFC from baseline
- Mean number of GdE lesions
- Mean number of new or enlarging T2-hyperintense lesions

Relapses were considered as count data and were summarized using a Poisson approach to obtain the relative ARR or rate ratio from the total number of relapses and patient-years. The analyses were performed using the Comprehensive Meta-Analysis software.

The heterogeneity between studies was assessed using I^2 statistics, which quantifies the percentage of variation across studies that is because of

heterogeneity rather than chance. Heterogeneity is considered to be low when I^2 is less than or equal to 25%, moderate when I^2 is between 25% and 75%, and high when I^2 is greater than or equal to 75%. Attempts were made to explain substantial statistical heterogeneity ($I^2 \geq 50\%$) by subgroup analyses or elimination of outliers. Where statistical heterogeneity remained present in the subgroup analyses, clinical outcomes were presented separately for each study and were reviewed qualitatively. The I^2 statistics, however, do not provide evidence about clinical heterogeneity in study design, treatments, and baseline demographics and characteristics of patient population.

The planned subgroup analyses included age (≤40 years or >40 years), baseline EDSS score (0 to 3, or >3), GdE lesions at screening (0 ≥ 1), gender (female or male), and number of relapses in the previous year before screening (1, 2, or ≥3).

Indirect Comparisons

Bayesian NMAs were conducted for two outcomes: relapse and disability. The selection of the outcome-specific measures for the NMA (the proportion of patients with sustained disability progression) was based on input from clinical experts. NMAs were not conducted for other efficacy outcomes (MRI findings and health-related quality of life) because data were sparsely reported, and, in the case of MRI, eight out of 14 studies reporting MRI outcomes were subsets of randomized populations with unclear selection criteria for MRI scans (see Table A10.2 in the clinical and economic report [see the "Availability of Companion Documents" field]). NMAs were not conducted for adverse events data (serious adverse events, and withdrawal because of adverse events) because the occurrence of events was low.

WinBUGS software (MRC Biostatistics Unit, Cambridge, UK) was used for all NMAs. Posterior densities for all unknown parameters were estimated using Markov Chain Monte Carlo methods. Prior distributions for overall effects of interest and study-specific effect estimates were assigned vague normal prior distributions centred at zero, with adequately large variances to allow the collected data to drive the calculation of pooled estimates. Model diagnostics including trace plots, autocorrelation plots, and the Brooks-Gelman-Rubin statistic were assessed to ensure model convergence. Assessment of model fit for NMA comprised the assessment of deviance information criterion and comparison of residual deviance to the number of unconstrained data points. Measures of effect were estimated according to the WinBUGS routine developed by the Evidence Synthesis Group, consisting of experts from the universities of Bristol and Leicester (the code is available from the website). Median estimates were reported, along with corresponding 95% credible intervals ([CrI]; Bayesian confidence interval). For comparative purposes, both fixed-effects and random-effects NMAs were conducted.

Regarding the interpretation of NMA estimates, if a 95% CrI for a risk ratio comparing two interventions did not include the value 1, this was interpreted as an indication that there is a less than 5% probability that there was no difference in effect between treatments.

For ARR

The Poisson distribution is a discrete distribution and is appropriate for modelling counts of observations or events that occur in a given interval of time (or space). In this review, ARR was modelled as a Poisson outcome based on the total number of relapses observed within a treatment group and the total number of person-years of follow-up for that treatment group as the input data.

Where studies did not report the total number of relapses or exposure time (person-years) directly in the publication, imputations were performed to derive the respective values. Missing total number of relapses were derived using exposure time (in person-years) and the reported mean ARR values. For missing exposure time (in person-years), the values were imputed using treatment duration and number of patients completing the study (100% was assumed in cases where the percentage of completers was not reported).

For Sustained Disability Progression

Patient sustained disability progression was analyzed as a binomial outcome, with the total number of patients with the event within a treatment group and the total number of patients randomized for that treatment group as the input data.

Exploring Heterogeneity

NMA requires that studies be sufficiently similar in order for their results to be pooled. A wide range of patient and trial characteristics were recorded to allow for a qualitative assessment of the heterogeneity of included trials. However, the methodological limitations with this approach are recognized; assessment of heterogeneity is naturally limited to reported characteristics. For example, older trials did not report or indicate whether the patient population consisted solely of treatment-naïve patients or was inclusive of patients with history of a prior treatment. Assumptions based on the reported information were made to that aspect; consequently, the ability to explore the impact of heterogeneity between studies regarding patient population, in terms of treatment experience, in the NMA was limited.

Heterogeneity was further explored through selected meta-regressions and subgroup analyses based on patient covariates (baseline EDSS score, time since symptom onset, number of relapses in previous year, prior-treatment history) and trial characteristics (publication date and treatment duration). Meta-regressions were performed when the variable was continuous in order to incorporate the maximum amount of information

available from trials. Subgroup analyses were performed when the variable could be dichotomized (e.g., patient population was treatment-naïve or mixed). Cut-offs defining the subgroups (e.g., trial publication date or treatment duration) were selected based on currently accepted conventions and clinical expert input.

Pharmacoeconomic Analysis

The analysis was in the form of a cost-utility analysis. The primary outcome was the number of quality-adjusted life-years (QALYs), with treatments compared in incremental cost per QALY (incremental cost-utility ratio [ICUR]).

See the clinical and economic report (see the "Availability of Companion Documents" field) for additional description of the pharmacoeconomic analysis performed.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The Canadian Drug Expert Committee (CDEC) is an advisory board to the Canadian Agency for Drugs and Technologies in Health (CADTH). It makes recommendations and provides advice to Canadian jurisdictions to use in making informed decisions. It is made up of experts in drug evaluation, drug utilization, and drug therapy, and public members.

Evidence-informed recommendations were developed by CDEC to address the following policy questions:

1. For patients with relapsing-remitting multiple sclerosis (RRMS), what are the preferred initial pharmacological treatment strategies?
2. For patients with RRMS, what are the pharmacological strategies for patients not adequately controlled on initial pharmacotherapy?
3. Should combination strategies be considered for treatment of patients with RRMS? If so, what are the appropriate treatment options?

The Committee considered the evidence and its limitations primarily from a population-based perspective. The anticipated absolute benefits, harms, and cost-effectiveness of the therapies compared with each other, along with patient group input, were considered to be fundamental in the development of system-level recommendations. The Committee also recognized that recommendations for treatment optimization related to the use of disease-modifying treatments have been developed by the Canadian Multiple Sclerosis Working Group and are based on clinical judgment and consideration of individual patient characteristics.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

Economic Evidence

The Committee considered the results of an economic model developed to assess the comparative cost-effectiveness among individual disease-modifying agents in relapsing-remitting multiple sclerosis (RRMS). The model was in the form of a cost-utility analysis, with treatments compared in terms of the incremental cost per quality-adjusted life-year (QALY) gained over a time horizon of 25 years. The target population was Canadians with RRMS, with a typical patient profile adopted from the randomized controlled trials (RCTs) identified in the systematic review: an average age of 36 years, gender distribution of 68% female, time since symptom onset of five years, and an initial discrete distribution of Expanded Disability Status Scale (EDSS) score with a mean score of 2.3. The analysis was conducted from the perspective of a provincial Ministry of Health in Canada.

The current treatments that are approved and available in Canada were included in the primary analysis: dimethyl fumarate 240 mg, fingolimod 0.5 mg, glatiramer acetate 20 mg/mL, interferon beta-1a 30 mcg, interferon beta-1a 22 mcg, interferon beta-1a 44 mcg, interferon beta-1b 250 mcg, and natalizumab 300 mg/15 mL. Emerging treatments in RRMS (alemtuzumab and teriflunomide) for which regulatory approval has not been granted were included in an exploratory analysis.

The annual costs for all treatments considered in the primary analysis are presented in Table 1 in the original guideline document.

A Markov cohort approach was taken for the analysis, based on a series of health states that reflect the progression of patients with RRMS. Health states were defined according to the EDSS (EDSS 0 to 2.5, 3 to 5.5, 6 to 7.5, 8 to 9.5, and 10), as well as severity of relapse (defined as mild/moderate or severe). During one cycle, patients could remain in the current health state; progress to the next, more severe state; improve to a less severe state; transition to a secondary progressive multiple sclerosis (MS); withdraw from treatment; or die. Because of limited clinical evidence, sequential use of treatments was not considered; therefore, the analysis assessed the cost-effectiveness of the treatments used as initial therapy only.

The progression to more severe states was based on natural history data for MS from London, Ontario, and British Columbia cohort studies. Treatment effects were based on network meta-analysis (NMA) for the outcomes of annualized relapse rate and sustained disability progression. The cost of managing RRMS and utility values for the health states were derived from published literature. A variety of deterministic and probabilistic sensitivity analyses as well as a value-of-information analysis were carried out.

In the base case, glatiramer acetate was the most cost-effective treatment, unless willingness to pay exceeds $118,242 per QALY, at which point interferon beta-1b 250 mcg was the most cost-effective treatment (see Table 2 in the original guideline document). The cost-effectiveness frontier (lines connecting the treatments that are not dominated) is comprised of glatiramer acetate, interferon beta-1b 250 mcg, dimethyl fumarate, and natalizumab. The sequential incremental cost-utility ratios (ICURs) of dimethyl fumarate versus interferon beta-1b was $425,655 per QALY and natalizumab versus dimethyl fumarate was $872,972 per QALY – not considered cost-effective initial treatments. Fingolimod and interferon beta-1a 30 mcg, 22 mcg, and 44 mcg were dominated by the treatments comprising the cost-effectiveness frontier.

Although the results of the probabilistic sensitivity analysis were consistent with the deterministic base case results, they indicated uncertainty regarding which treatments are cost-effective depending on the willingness-to-pay threshold. When the decision-maker is willing to pay a maximum of $50,000 per QALY ($\lambda$ = $50,000), glatiramer acetate was the cost-effective treatment in 70% of replications, followed by interferon beta-1b (Extavia) in 26% and beta-1b (Betaseron) in 3% of replications. When the decision-maker is willing to pay a maximum of $100,000 per QALY ($\lambda$ = $100,000), glatiramer acetate was the cost-effective treatment in 42% of replications, followed by interferon beta-1b (Extavia) in 38% and beta-1b (Betaseron) in 11%.

Based on the deterministic sensitivity analyses conducted, the results were most sensitive to data inputs for treatment effects of disability progression and drug costs. Other inputs, such as RRMS-related treatment costs, the natural history of disease progression, the model time horizon, and the stopping rule were shown to impact ICURs, as well. Influence of patient baseline characteristics were also assessed in sensitivity analyses: ICURs decreased for younger patients and for patients with higher baseline EDSS score. With the exception of treatment effects of disability progression and drug costs, none of these analyses changed the conclusion from the base case scenario.

The clinical evidence was sufficient to support the inclusion of combination therapy in the economic model; therefore, the cost-effectiveness of combination therapy in RRMS remains unknown.

Method of Guideline Validation

External Peer Review

Description of Method of Guideline Validation

A broad range of stakeholders was invited to provide feedback on the guidelines document.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

The recommendations are based on clinical (systematic reviews of randomized controlled trials, network meta-analysis, and individualized randomized controlled trials [RCTs]) and cost-effectiveness evidence.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Optimal use of drug therapies for relapsing-remitting multiple sclerosis (RRMS) that results in improved health outcomes and is cost-effective

Potential Harms

In safety assessments, there were no differences in the overall incidence of adverse events that would favour any particular agents. Each agent had specific adverse events such as influenza-like symptoms and injection-site reactions for the interferons; hypersensitivity and injection-site reactions for glatiramer acetate; infusion reactions and risk of progressive multifocal leukoencephalopathy (PML) for natalizumab; infusion reactions, thyroid disorders and infection for alemtuzumab; cardiovascular disorders (bradycardia, atrioventricular block) for fingolimod; hair loss for teriflunomide; and flushing for dimethyl fumarate. Liver enzyme elevation and gastrointestinal disorders occurred with many treatments but appeared to be transient. Serious adverse events and death were rare in all trials and did not differ statistically between treatments. There were no apparent differences between combination therapy and monotherapy in safety events.

Treatment-specific Adverse Events

- *Interferon beta (Betaseron, Rebif, Avonex)*: injection site reactions, flu-like symptoms, liver enzyme elevation (Betaseron, Rebif)
- *Glatiramer acetate*: injection site reactions, hypersensitivity
- *Natalizumab*: infusion reactions, skin disorders (rash, dermatitis, pruritus)
- *Alemtuzumab*: fatigue, infection, skin disorders, thyroid disorders
- *Fingolimod*: liver enzyme elevation, gastrointestinal disorders (nausea, vomiting, diarrhea), cardiovascular disorders (bradycardia, atrioventricular block)
- *Teriflunomide*: liver enzyme elevation, gastrointestinal disorders (nausea, vomiting, diarrhea), hair thinning or decreased hair density
- *Dimethyl fumarate*: flushing, gastrointestinal disorders (nausea, vomiting, diarrhea), liver enzyme elevation

Contraindications

Contraindications

Contraindications of Health Canada-Approved Therapeutic Options of Interest Based on Product Monographs

- *Interferon beta-1a*: contraindicated in patients with known hypersensitivity to natural or recombinant interferon, patients with liver disease, pregnant women
- *Interferon beta-1b*: contraindicated in patients with known hypersensitivity to natural or recombinant interferon, patients with liver disease, pregnant women
- *Glatiramer acetate*: contraindicated in patients with known hypersensitivity to glatiramer acetate or mannitol
- *Natalizumab*: contraindicated in patients who have had progressive multifocal leukoencephalopathy (PML), at risk for PML; hypersensitive to this drug or to any ingredient in the formulation or any component of the drug; immunocompromised, including those immunocompromised due to immunosuppressant or antineoplastic therapies, or immunodeficiencies
- *Fingolimod*: contraindicated in patients who are hypersensitive to fingolimod, who are at risk for an opportunistic infection (immuno-compromised due to treatment or to disease), have hepatic insufficiency, active severe infections, or known active malignancies
- *Dimethyl fumarate*: contraindicated in patients who are hypersensitive to dimethyl fumarate

Note: While only the interferons have specific product monograph contraindications for pregnancy, animal studies of fingolimod show potential teratogenicity. It is unclear as to whether natalizumab is safe during pregnancy; and although it is unclear whether glatiramer acetate is safe during pregnancy, it is not recommended for use in pregnant women.

Qualifying Statements

Qualifying Statements

- The information provided in the recommendations report neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.
- The Canadian Agency for Drugs and Technologies in Health (CADTH) is not legally responsible for any damages arising from the use or misuse of any information contained in or implied by the contents of this document.
- The statements, conclusions, and views expressed in the recommendations report do not necessarily represent the view of Health Canada or any provincial, territorial, or federal government, or the manufacturer.
- At the time of this report, alemtuzumab and teriflunomide were not approved by Health Canada for the treatment of relapsing-remitting multiple sclerosis (RRMS). Therefore, while the science reports included alemtuzumab and teriflunomide in addition to interferon beta-1a, interferon beta-1b, glatiramer acetate, natalizumab, fingolimod, and dimethyl fumarate, the recommendations presented in this report apply at present only to the aforementioned treatments that are approved for RRMS in Canada.

Limitations of the Evidence

- There were a limited number of randomized controlled trials (RCTs) directly comparing treatments for RRMS, necessitating indirect treatment comparisons using network meta-analyses (NMAs). Indirect treatment comparisons, based on the NMA of studies conducted over a 20-year time period, were complicated by the heterogeneity of study and patient characteristics; control of these characteristics was limited by the small number of studies in relation to the number of treatment strategies.
- A key limitation of the review was the inability to estimate relative treatment effects based on prior treatment history, as in the majority of monotherapy trials either the patients' prior treatment history was unclear, or the trial included a mixture of treatment-naïve and treatment-experienced patients.
- An additional limitation included the relatively short duration of RCTs, which does not allow for between-treatment comparisons of effects on long-term disability. In addition, there were limited quality of life data to support comparisons between treatments, including comparisons of oral and injectable therapies.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Quick Reference Guides/Physician Guides

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Canadian Agency for Drugs and Technologies in Health (CADTH). Recommendations for drug therapies for relapsing-remitting multiple sclerosis. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health (CADTH); 2013 Oct. 19 p. [44 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2013 Oct

Guideline Developer(s)

Canadian Agency for Drugs and Technologies in Health - Nonprofit Organization

Source(s) of Funding

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Guideline Committee

Canadian Drug Expert Committee (CDEC)

Composition of Group That Authored the Guideline

Committee Members: Dr. Robert Peterson (*Chair*), Dr. Lindsay Nicolle (*Vice-Chair*), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Ms. Cate Dobhran, Mr. Frank Gavin, Dr. John Hawboldt, Dr. Peter Jamieson, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. James Silvius, and Dr. Adil Virani

Financial Disclosures/Conflicts of Interest

Conflicts of interest: None

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Electronic copies: Available from the Canadian Agency for Drugs and Technologies in Health (CADTH) Web site .

Availability of Companion Documents

The following are available:

- Comparative clinical and cost-effectiveness of drug therapies for relapsing-remitting multiple sclerosis. Clinical and economic report. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health (CADTH); 2014 Mar. 295 p. (CADTH Therapeutic Review; vol. 1, no. 2b). Electronic copies: Available from the Canadian Agency for Drugs and Technologies in Health (CADTH) Web site .
- Comparative clinical and cost-effectiveness of drug therapies for relapsing-remitting multiple sclerosis. Project protocol. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health (CADTH); 2012 Dec. 8 p. (CADTH Therapeutic Review; vol. 1, no. 2A). Electronic copies: Available from the CADTH Web site .
- Drug therapies for relapsing-remitting multiple sclerosis. Project in brief. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health (CADTH); 2013 Nov. 1 p. (CADTH Therapeutic Review). Electronic copies: Available from the CADTH Web site .
- Patient group input to CADTH submitted by the Multiple Sclerosis Society of Canada. 2013 Mar 28. 6 p. Electronic copies: Available from the CADTH Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on August 27, 2014. The information was verified by the guideline developer on September 9, 2014. This summary was updated by ECRI Institute on December 3, 2014 following the U.S. Food and Drug Administration (FDA) advisory on Tecfidera (dimethyl fumarate). This summary was updated by ECRI Institute on August 11, 2015 following the U.S. Food and Drug Administration advisory on Gilenya (fingolimod).

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